1 Examiner has objected to the language "the chemical compounds are not intermediates leading to a single final product" for lack of support. In addition, the Examiner has objected to language found in claims 2 and 3 including the limitations "first [and additional] set of reagents or reaction conditions", "first [and second] specific spatial period", and "first [and additional] set of compounds" where each compound within the set "being related to all other compounds in the first [or additional] set as a product of the first set of reagents or reaction conditions." The Examiner states that there does not appear to be support for these specific limitations and requests that the Applicant specifically point to support for these limitations within the Specification. Applicant respectfully disagrees that these added limitations constitute new matter and below points to support for these limitations in the Specification as originally filed.

For the language "the chemical compounds are not intermediates leading to a single final product," Applicant would first like to draw the Examiner's attention to Figures 1-3 depicting the synthesis of a combinatorial library on a thread thereby illustrating the claimed invention. As one of skill in the art would appreciate, the compounds of the linear array are not intermediates at various stages in the synthesis of one final product. The compounds of the claimed invention are rather fully synthesized compounds. In other words, one could not take the compounds of the array and subject them to additional reactions and arrive at the same final product. The compounds of the array are each final products *per se*. Further support for this idea can be found starting on page 9, line 26 and continuing to page 11 describing the preparation of the claimed invention and on page 17, line 26, and continuing to page 21 describing an actual preparation of a linear array of peptides on a string. Nowhere in the application is described the idea of creating diversity in the library by halting the synthesis of the combinatorial library in the midst of the step needed to create the full library. In contrast, the compounds of the claimed arrays are all approximately the same size. For example, in the case of a polypeptide library, all the polypeptides will have approximately the same number of amino acids. A claimed polypeptide array would not include a first compound that is a single amino acid and a second compound that is a 20-mer. Applicant respectfully submits that the new matter rejection be removed in light of the support for this limitation in the Specification as originally filed because clearly one of

ordinary skill in the art reading this application would realize that the Applicant was not trying to claim an array of intermediates along a pathway leading to a single final product.

In the present Amendment, Applicant has further amended the claims to recite that the chemical compounds of the array are members of a combinatorial library and that each compound is represented in the array at least twice at discontinuous portions of the array, support for which can be found throughout the Application including the Background of the Invention section, the Drawings, and in the Experimental Details beginning on page 22. Specifically, support for the idea that each compound is represented at least twice within the array can be found on page 11, lines 20-21, and on page 16, lines 21-24, which describe the various compound repeat times of different libraries. Applicant respectfully submits that these new limitations are supported by the Specification and would be recognized by one of ordinary skill in the art reading the Specification.

Support for the various language in claims 2 and 3 recited by the Examiner in her new matter rejection can be found starting on page 9, line 26 and continuing to page 11 describing a typical preparation of the claimed invention. Further support for the language in the claims at issue can be found starting on page 22, line 25, and continuing to page 23, line 7, and Figures 1-3. In view of the support for claims 2 and 3, Applicant requests that the rejection be removed.

II. **Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.** Claims 1, 3, and 4 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Applicant submits that claim 1 as amended obviates the present rejection. However, Applicant would like to add that the language "the chemical compounds are not intermediates leading to a single final product" would be clear to one of ordinary skill in the art reading the claims in light of the Specification. As described above, the claimed invention includes an array of "final products" not an array of intermediates along a synthetic pathway leading to one final product as described by Lebl *et al.* in EP 0 38 433.

Applicant has also been asked to clarify the antecedent basis in claim 3 which recites "reactive functional groups" and in claim 4 which recites "reactive moieties" and "additional functional groups." Claims 3 and 4 have been amended to obviate this rejection. As would be appreciated by one of skill in this art, the synthesis of the array begins with a support having various functional groups on it. The support is then wrapped around a template and the surface of the template with the support wrapped around it is divided lengthwise into regions. Each region is then subjected to various reagents or reaction conditions to either add a reactive moiety onto a functional group of the support or to modify a functional group. In subsequent steps in the preparation of the array, the reactive moieties previously attached to the support through a reactive functional group on the support, or previously modified functional groups are used to attach other reactive moieties or are further modified. Through successive iterations the members of the combinatorial library are synthesized.

To give but one example, imagine a support having activated esters as the reactive functional groups. In step (d), the activated esters could be used either to attach a reactive moiety with a primary amine group for attaching the moiety to the ester and an amide group, for further functionalization along certain regions of the support, or to reduce the activated ester to a primary alcohol along other regions of the support. Subsequently, the reactive moiety with the amide might be further functionalized to attach another reactive moiety through an amide linkage or it might be reduced to form an alcohol. Also, the primary alcohol created from the reduction of the activated ester might be alkylated thereby further modifying this functional group. This is but one illustration of the myriad of reactions and reagents that could be used to synthesize the claimed array.

Applicant submits that claims 3 and 4 in light of the Specification and the above illustration would be clear to one of ordinary skill in this art and, therefore, requests that the rejection be removed.

III. **Rejection under 35 U.S.C. § 102(b), as being anticipated by EP 0 385 443**. Claims 1-7, 37, 38, and 42 stand rejected under 35 U.S.C. § 102(b) as being anticipated by EP 0 385 443 by Lebl *et al.* Examiner takes the position that Lebl *et al.* describe at least two different chemical

compounds attached to a linear support. However, the only way to have at least two different chemical compounds attached to the support in the system of Lebl *et al.* is if one stops the synthesis in the middle. In such a circumstance, all products on the support are necessarily related as intermediates on route to the synthesis of a single final product. Lebl *et al.*, of course, acknowledges that they teach only a method of "obtaining some or all intermediates and eventually also the desired final product" (page 3, line 54). Thus, Lebl *et al.* do *not* teach a method of forming an array of at least two different chemical compounds wherein the chemical compounds are not intermediates leading to a single final product, as recited in amended claim 1. Support for claim 1 can be found in Figures 1-3, and on page 9, starting at line 26, to page 11 as discussed above. Furthermore, one of skill in this art reading the present application would immediately appreciate that it is directed to arrays of compounds that are not related to each other as intermediates leading to a single final product. Each of the compounds of the arrays of the claimed invention is a final product in and of itself. Further processing would not lead to a common final product as is taught by Lebel *et al.*

Therefore, EP 0 385 443 does not teach a linear array of chemical compounds as recited in claim 1 of the present Application as amended herewith, and Applicant respectfully requests that the rejection be removed.

Nor does Lebl *et al.* teach the invention recited in claim 2 or 3, which also recite "wherein the chemical compounds are members of a combinatorial library." Each of these claims recites a linear array produced by a process that necessarily creates a linear array in which compounds that are related to each other as products of identical reaction conditions are simultaneously generated at multiple positions along the array. In Lebl *et al.*, because the linear support is pulled through a series of reaction conditions, every compound on the support is produced in an identical series of reactions; therefore, the teaching of Lebl *et al.* would not produce the claimed invention, wherein the members of a combinatorial library are produced as a linear array along a support. Products resulting from a single set of reaction conditions are not separated from one another on the array by a specific spatial period, as recited in the present claims, but rather are arranged continuously along the support. Accordingly, Lebl *et al.* cannot anticipate the invention recited in independent claims 2 and 3.

IV. Rejection under 35 U.S.C. § 102(b), as being anticipated by Browne *et al.* Claims 1-3, 5-7, 27, and 42-46 have been rejected under 35 U.S.C. § 102(b), as being anticipated by Browne *et al.* (*Anal. Chem.* 68:2289-2295, 1996). Examiner states that Browne *et al.* disclose an "instrinsic sol-gel clad fiber optic sensor" which anticipates the claimed array of at least two chemical compounds attached to a support. Applicant submits that the amended claims of the present invention are directed to a linear array of chemical compounds, wherein the chemical compounds are members of a combinatorial library. Since Browne *et al.* does not teach any type of combinatorial library but instead is limited to chemical sensors, Browne *et al.* cannot anticipate the claimed invention. In addition, Browne *et al.* do not teach or suggest that each chemical sensor occurs on the optical fiber at least twice at discontinuous regions of the fiber. Given these differences between the teachings of the cited art and the claimed invention, Applicant requests that the rejection be removed.

V. Rejection under 35 U.S.C. §103, as being unpatentable over Lebl *et al.* (EP 0 385 443) or Browne *et al.* (*Anal. Chem.* 1996) in view of Lebl *et al.* (US 5,688,696). Claims 1-7 and 37-46 have been rejected under 35 U.S.C. § 103(a), as being unpatentable over Lebl *et al.* (EP 0 385 443) or Browne *et al.* (*Anal. Chem.* 1996) in view of Lebl *et al.* (US 5,688,696). The teachings of two of these references have been discussed above, and Applicant submits that the amended base claims to a linear array of at least two chemical compounds with the limitation, "wherein the chemical compounds are not intermediates leading to a single final product," "wherein the chemical compounds are member of a combinatorial library," and wherein each chemical compound is represented within the array at least twice at discontinuous regions of the array is not taught or suggested by any of the cited references even when they are combined. Since Lebl *et al.* (EP 0 385 443) is limited to synthesizing one particular oligomer on a band and Browne *et al.* is limited to chemical sensors, neither reference even in view of Lebl *et al.* (U.S. 5,688,696) can teach the claimed invention of a combinatorial library of compounds that are not intermediates leading to a single final product arranged as a linear array, in which each compound is represented at least twice.

One of the advantages of having the compounds of the combinatorial library represented more than once in the linear array is that the whole array can be analyzed quickly and accurately using Fourier transform analysis for specific structure-function relationships. This is quite elegantly demonstrated by the experiments described in the application starting on page 22. Using a linear array as a method of organizing a combinatorial library allows one to evaluate the full library. This is one of the major goals of combinatorial chemistry—to be able to produce millions of chemical compounds and fully analyze the library for compounds with a desired property. Also, the analysis includes the ability to determine which structural features within the library increase or decrease the desired property. Up until the work of Schwabacher, no one was able to screen an entire combinatorial library for detailed structure-function data. Schwabacher's use of linear arrays and Fourier transform combinatorial chemistry allowed combinatorial chemists to finally realize this long sought goal in combinatorial chemistry.

None of the cited references even in combination would lead to the ground-breaking invention of linear arrays of combinatorial libraries which can be produced and analyzed in a manner not available to standard two-dimensional arrays of combinatorial libraries. In light of this important contribution to the field of combinatorial chemistry, Applicant is entitled to the broadest scope possible.

In light of the fundamental differences between what is claimed in the present application and the teachings of the cited references as well as the lack of motivation to combine these references, Applicant requests that the rejection under § 103 be removed.

VI. **Double Patenting.** Claims 1-7 and 37-46 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6-13, and 30-50 of co-pending Application, U.S.S.N. 09/535,300. Applicant respectfully refrains from addressing this issue until such time as the rejection matures from a provisional rejection to an actual rejection.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on 11/8/02

Appendix A

Marked Up Versions of New Paragraphs

On page 6, beginning at line 3:

"Thread": As used herein, "thread" is a substantially one-dimensional support which supports synthetically useful sites for the attachment of a chemical library. The thread may take the physical form of a monofilament, a braided or wound assembly of filaments, a tape, hollow tube, or the like. The thread may be of any material that provides adequate physical, chemical, and mechanical properties. Suitable materials may be, but are not limited to, cotton, polyamide, polyester, acrylic, teflon, glass, steel, KEVLAR® fibers (aromatic polyamide fibers), and the like. Examples of relevant properties are tensile strength, elastic modulus, and inertness to the anticipated chemical treatments. The thread itself may be chemically modified so as to permit attachment of library members, covalently or otherwise, or the thread may support a continuous or discontinuous solid phase support for synthesis, as for example a series of beads arrayed along the thread, a grafted polymer layer, or a gel phase coated upon or impregnated into the thread. Many methods of functionalizing various materials and surfaces for use as synthesis supports are known in the art.

On page 8, beginning at line 18:

As one of ordinary skill in the art will realize, the support or thread may comprise any material upon which an array of compounds may be synthesized or attached, and that provides the desired physical, chemical and mechanical properties. Specific examples of relevant properties include, but are not limited to, tensile strength, elastic modulus, and inertness to the anticipated chemical treatments. In certain embodiments, this support comprises simply one material. In other embodiments, this support or thread is a composite material, that is, comprises a combination of one or more materials in any possible form. Examples of particularly preferred materials for use single material or composite supports include, but are not limited to, cotton, polyamide, polyester, acrylic, teflon, glass, steel, KEVLAR® fibers (aromatic polyamide fibers), metal, and the like, or any combination of one or more appropriate materials.

On page 21, beginning at line 22:

The data obtained from the thread reading was reduced to 2 points per compound, as outlined above (one point for each signal, taken as the average rise above the valley on either side of the signal, and one point between each peak). The Fourier transformation was done using a basic program using standard algorithms (Lynn et al., *Introductory Digital Signal Processing with Computer Applications*; Wiley: Chichester, 1989.; Press et al., *Numerical Recipes in C: The Art of Scientific Computing*; 2 ed.; Cambridge Univ. Pr.: Cambridge, 1993.; Blahut, R.E. Fast Algorithms for Digital Signal Processing 1985[.; http://theory. lcs. mit.edu/~fftw/; http://www.speech.cs.cmu.edu/comp.speech/Section 2/Q2.4.html]). In a preferred embodiment, the FT should be resonant: a radix 2 algorithm is less appropriate, and would require oversampling of data. The "waveform" corresponding to efficacy of particular amino acids installed on a given cylinder was extracted as follows. The real and imaginary parts of the peak at the relevant frequency were extracted from the frequency domain, as were all harmonics. These values were then put into a smaller array and fourier transformed back to the time domain. The resulting "waveform" represents the output signal for each of the functional groups added on that cylinder. The signal for the 35 compound library, shown in Figure 7, was Fourier transformed, and the waveforms corresponding to the 5 and 7 cm cylinders were extracted from the FT spectrum. These waveform binding profiles are shown in Figure 8.